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THE USE OF PHARMACEUTICALLY ACTIVE COMPOUNDS THAT BLOCK THE 5-HT_{2A}
RECEPTOR

[Het gebruik van farmaceutisch werkzame verbindingen die de 5-HT_{2A} receptor blokkeren]

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INVENTORS	(72):	Dr. Marcel David Waldinger and Dr. Dave Henry Schweitzer
APPLICANTS	(71):	Dr. Marcel David Waldinger and Dr. Dave Henry Schweitzer
TITLE	(54):	THE USE OF PHARMACEUTICALLY ACTIVE COMPOUNDS THAT BLOCK THE 5-HT2A RECEPTOR
FOREIGN TITLE	[54A]:	Het gebruik van farmaceutisch werkzame verbindingen die de 5-HT2A receptor blokkeren

Title of the invention: The use of pharmaceutically active compounds that block the 5-HT_{2A} receptor

Prostate cancer is the most frequently occurring cancer in western men (van der Gulden et al., 1994). The prevalence hereof increases perceptibly with advancing age (Dunsmuir, 1998). Clinically manifest prostate cancer seldom occurs in men who are younger than 50 years of age. 93% of the patients who die as a result of prostate cancer are older than 65 years.

The treatment of prostate cancer comprises surgical or chemical castration. Orchiectomy (i.e., the removal of both testicles) reduces the quantity of plasma testosterone by approximately 90%. The adrenals produce the remaining 10% of the plasma testosterone. However, orchiectomy reduces the concentration of dihydrotestosterone, the active metabolite of testosterone, by only 60%. Thus orchiectomy is usually combined with a complete androgen blockade in order to reduce the production of testosterone by the adrenals as well (maximum androgen blockade: MAB).

The medical (hormonal) treatment of prostate cancer comprises the administration of LH-RH agonists, antiandrogens or a combination of the administration of antiandrogens and orchiectomy. Treatment with LH-RH agonists leads to a low plasma concentration of testosterone after approximately 3 weeks of treatment. In terms of binding to androgen receptors, the antiandrogens such as flutamide, nilutamide and bicalutamide act competitively in regard to dihydrotestosterone, whereby this leads to a reduced negative feedback in terms of LH-RH production. This means that the concentration of testosterone will increase as a consequence of increased LH-RH production and hence LH production. Thus it is very important that these medicines be combined with LH-RH agonists in order to be certain that testosterone is no longer present in the blood, whereby this could otherwise encourage prostate tumor growth. It is in this way that MAB is capable of amplifying the effects of castration following orchiectomy.

However, many patients who have undergone orchiectomy or who are being treated with LH-RH agonists or who undergo a combination of these treatments with antiandrogens develop problems with hot flashes ("hot flashes" [sic]), reduced libido, erectile disorders, gynecomastia and reduced energy (Radlmaier et al., 1990).

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Although hot flushes are not life threatening, they can be very inconvenient and annoying. They often lead to a considerably reduced quality of life for men who are afflicted with them (Frodin et al., 1985).

As a consequence of a dearth of epidemiological research in this area, the prevalence of these hot flushes has not so far been well recognized in men.

A clinically relevant reduction in severe hot flushes and the associated sudation attacks has now been found in men.

Although the applicants do not wish to be linked to any particular theory, the occurrence of hot flushes in men who have been subjected to orchiectomy or who are being treated with drugs that diminish testosterone or that block testosterone receptor[s] could be a consequence of a reduction in the concentration of plasma testosterone. Testosterone is transformed into dihydrotestosterone and estradiol. Hence a reduction in the plasma concentration of testosterone probably leads to a reduction in the plasma estrogens concentration as well.

Neuroendocrine studies suggest that the internal regulation of body temperature is brought about in the hypothalamus (Rebar and Spitzer, 1987), whereby this contains a large quantity of estrogen containing neuróns (Bloom, 1998). Moreover, it has been demonstrated that neuronal estrogen concentrations are associated with serotonin (5-hydroxytryptamine: 5-HT) neurotransmission (Stahl, 1998). Flushes could be mediated via these pathways, possibly under the influence of 5-HT_{2A} and 5-HT_{2C} receptor interactions.

* [Numbers in right margin indicate pagination of the original text.]

According to the applicants, the hypothetical involvement of 5-HT_{2A} receptors could also be substantiated by the fact that it has been demonstrated in animal experimental studies with rats that hyperthermia arises as a consequence of 5-HT_{2A} stimulation (Mazzola-Pomietto et al., 1995). Moreover, it has been found in humans that the administration of meta-chlorophenylpiperazine (mCPP), which is a 5-HT_{2C/2A} receptor agonist, can lead to sweating and heart palpitations (Kahn et al., 1990).

The reduction in plasma testosterone concentration and hence also the reduction in estrogen concentration induced in the patients, probably lead to activation of the 5-HT_{2A} receptor.

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The invention therefore pertains to the use of pharmaceutically active compounds that block the 5-HT_{2A} receptor and that additionally have an intrinsic effect on the postsynaptic 5-HT_{2A} receptor (an inverse 5-HT_{2A} agonistic action) for the manufacture of a drug for oral administration for use in the treatment of symptoms that are generated as a result of orchiectomy, or as a result of plasma testosterone reducing drugs, or testosterone receptor blocking drugs.

The pharmaceutically active compound preferably comprises mirtazapine and/or mianserin as such or in the form of a salt or in the form of a pharmacologically active metabolite thereof.

It is noted that mirtazapine or (RS)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino(2,1-a)pyrido(2,3-c)(2)benzazepine is known as an antidepressant. It is also known that mirtazapine possesses postsynaptic 5-HT_{2A} and 5-HT_{2C} blocking properties.

Mianserin, or 2-methyl-1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepine, is also known as an antidepressant but, by contrast, it has an α_1 receptor blocking effect.

It is additionally noted that hot flushes occur in women as well, though these then have a completely different cause, namely as a component of the menopausal syndrome that is related to reduced estrogen production in the body (Utian, 1972).

Mirtazapine can perhaps reduce hot flushes in menopausal women as well, but a double-blind, placebo-controlled study of this has not yet been carried out at the present time (Tome and Isaac, 1998).

Thus, in men, mirtazapine and mianserin reduce hot flushes that are induced via a low testosterone concentration, whereby this is probably a result of their 5-HT_{2A} receptor blocking properties. Both mirtazapine and mianserin have a 5-HT_{2A} receptor blocking effect. They differ from other 5-HT_{2A} receptor blocking compounds, such as ketanserin for example, by virtue of their intrinsic action on the 5-HT_{2A} receptor, so-called inverse 5-HT_{2A} agonism.

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The cases that are illustrated in the following examples will elucidate the invention, though without limiting the scope of patent protection thereof.

Example 1

A 65-year-old man had been suffering from depressive feelings, indifference and fatigue. These somber feelings gradually arose over a period of 4 months following orchiectomy as a consequence of prostate cancer. He had also suffered from hot flushes and the associated sudation attacks since his orchiectomy.

Mirtazapine was prescribed at a quantity of 30 mg/day. After two weeks, the patient reported that he had developed a marked decrease in the frequency and intensity of his hot flushes and sudation attacks. A clinical improvement occurred after just two days following the start of the treatment with mirtazapine. The treatment was stopped after two months. The hot flushes and sudation attacks recurred within 1 week after stopping the mirtazapine. The renewed administration of 30 mg/day mirtazapine again resulted in the disappearance of the hot flushes and the sudation attacks after a period of 2 days.

Example 2

A 72-year-old man had been suffering from decreased libido, erectile disorders and sudation attacks following a combination of orchiectomy and MAB, whereby this was achieved by combining LH-RH therapy with flutamide in order to block the androgen receptors. 30 mg/day Mirtazapine was prescribed for the patient in order to help him become free from his hot flushes and sudation attacks. After 1 week of treatment, he reported that he had experienced a significant reduction in the frequency and intensity of his hot flushes and sudation attacks. He continued for 6 months with the ingestion of 30 mg/day mirtazapine with no recurrence of hot flushes and sudation attacks.

Example 3

A 73-year-old man had been suffering over a period of 14 months from hot flushes and sudation attacks that had arisen 2 weeks following orchiectomy for prostate carcinoma. These hot flushes were present in such a frequent and severe manner both during the day and at night that he began to avoid social contacts. Endocrine paroxysmal syndromes were ruled out. The patient was prescribed 15 mg/day mirtazapine. The flushes and sudation attacks were reduced in a clinically relevant manner within a period of 1 week.

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An increase in dosage to 60 mg/day mirtazapine resulted in the complete disappearance of the hot flushes within a period of 4 weeks.

Stopping the ingestion of 60 mg/day mirtazapine once again led to the occurrence of the flushes within a period of 4 days. Renewed ingestion of 15 mg/day mirtazapine again resulted in the disappearance of the flushes and sudation attacks within a period of 2 days. Continuation of 30 mg/day mirtazapine over a period of 8 months has not led to the recurrence of the flushes.

Example 4

A 64-year-old man had been suffering from severe hot flushes and sudation attacks for two years following orchiectomy for the treatment of his prostate cancer. Endocrine paroxysmal syndromes were ruled out. The patient was treated with 15 mg/day mirtazapine. He reported that he had experienced a significant reduction in hot flushes within a period of 3 days following the start of the treatment. The use of 15 mg/day mirtazapine over a period of 6 months did not lead to the recurrence of the hot flushes.

Example 5

A 66-year-old man had been suffering from hot flushes and the associated sudation attacks for 4 months following orchiectomy for the treatment of his prostate cancer. Endocrine paroxysmal syndromes were ruled out. The patient was treated with 30 mg/day mianserin. He reported that he had experienced a considerable reduction in his hot flushes within 1 week following the start of the treatment. The use of 30 mg/day mianserin over a period of 3 months has not led to the recurrence of the flushes.

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Claims

1. The use of pharmaceutically active compounds that block the 5-HT_{2A} receptor and that additionally have an intrinsic effect on the postsynaptic 5-HT_{2A} receptor for the manufacture of a drug for oral administration for use in the treatment of symptoms that are generated as a result of orchiectomy, or as a result of plasma-testosterone reducing drugs, or testosterone receptor blocking drugs.
2. Use in accordance with Claim 1, whereby the pharmaceutically active compound comprises mirtazapine and/or mianserin as such or in the form of a salt, or in the form of a pharmacologically active metabolite thereof.
3. Use in accordance with Claim 1 or 2, whereby the symptoms comprise hot flushes and intensified sudation attacks.
4. Use in accordance with one or more of Claims 1-3, whereby the drug comprises a unit dosage of 15-60 mg/day, and preferably 15-30 mg/day mirtazapine or mianserin.
5. Use in accordance with each of the preceding claims, whereby the drug is administered in such a way that a dosage of 30 mg/day mirtazapine is administered at the rate of 30 mg/day twice daily with a time period in between of at least 6 h.

REPORT CONCERNING THE EXAMINATION OF THE PRIOR ART

Relevant literature			
Category	Citation of literature with an indication, to the extent necessary, of portions of text or figures of special relevance	Relevant for Claim No(s):	International Patent Classification (IPC)
A	PubMed, PMID: 9106912, UI: 97260793 Psychopharmacology March 1997, vol. 130(2), pages 144-151 (P. Mazzola-Pomietto et al.; Nat.Inst.Mental Health, Bethesda, * summary *	1-4	A61K 31/55 A61P 05/04 A61P 25/24
A	US 4,804,663 (L.E.J. Kennis and J. Vandenberg; Janssen Pharmaceutica N.V.) February 14, 1989 * column 9, lines 11-33 *	1	Technology sectors examined, defined in accordance with IPC 7
T	DE-A-19.821.926 (G. Laakman) November 18, 1999 * column 1, lines 37-46 and lines 54-55; column 2, lines 8-12 *	1-5	A61P 05 A61P 25/24
A	Repertorium 98/99, 1998, Nefarma, Utrecht * page 1092, Remeron (mirtazapine) * * page 1100, Tolvon (mianserin hydrochloride) *	4-5 4	Computer files
			Epodoc PAJ WPI PubMed
In the event that modified claims have been submitted, this report pertains to the claims that were submitted on:			Category designation statement: see separate page
Scope of the examination: full			
Claims examined:			
Claims that were not (fully) examined, with reasons:			
Date on which the examination was completed: April 3, 2000		Lead examiner: Dr. M.M. van Leijen	

Category of the cited literature:

- X: prior art that is of special relevance when considered on its own
- Y: prior art of special relevance when combined with other cited literature
- A: relevant prior art that does not form part of category X or Y
- O: with reference being made to unwritten prior art
- P: literature that was published between the priority and filing date
- T: literature published in an untimely manner on the theory or principle that forms the underlying basis of the invention
- E: colliding patent application
- D: designated in the application
- L: literature cited for other reasons
- &: member of the same patent family; corresponding literature

APPENDIX THAT FORMS PART OF THE REPORT CONCERNING THE EXAMINATION OF
THE PRIOR ART, CARRIED OUT ON PATENT APPLICATION NO.: 1012954

The appendix contains a compilation of patent applications or patents that were published elsewhere (so-called members of the same patent family) that are in conformity with the patent documents designated in the report.

The compilation was assembled on the basis of data from the computer file of the European Patent Office on April 11, 2000.

The correctness and completeness of this compilation is guaranteed neither by the European Patent Office nor by the Office for Industrial Property; the data are provided for information purposes.

① In het rapport genoemd octrooi- geschrift	② datum van publicatie	③ overeenkomend(e) geschrift(en)	④ datum van publicatie
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Key: 1 Patent document cited in the report

2 Publication date

3 Conforming document(s)

4 Publication date

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① In het rapport genoemd octrooi- geschrift	② datum van publicatie	③ overeenkomend(e) geschrift(en)	④ datum van publicatie
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